Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-33 and 35-42 are pending in the application with claims 1 and 17 being the independent claims. The Examiner has withdrawn claims 3-7, 11-12, 15-16, 21-27, 30-33, 35, 37 and 42 from consideration.

Claims 1-2, 8, 13, 14, 17-20, 28, 36 and 38-41 have been rejected.

Claims 9, 10, and 29 are objected to, but the Examiner has indicated that they would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims.

Based on the following remarks, Applicant respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Withdrawn Claims 3-7, 11-12, 15-16, 21-27, 30-33, 35, 37 and 42

The Examiner has indicated that claims 3-7, 11-12, 15-16, 21-27, 30-33, 35, 37 and 42 have been withdrawn from consideration. (Paper No. 45, page 2.) Claims 3-7, 11-12, 15-16, 21-27, 30-33, 35, 37 and 42 are drawn to species of generic claims. As indicated in Applicants' Reply to Requirement for Election of Species, filed March 9, 2000, Applicants assert the right to claim additional species in the event that a generic claim thereto is found allowable in accordance with 37 C.F.R. § 1.141(a). Applicants assume that if the Examiner fails to find any prior art to the elected species, he will extend the search further into the genus. If upon further examination the generic claim is found allowable, it is respectfully submitted that the additional species within the genus should also be deemed allowable.

Rejections under 35 U.S.C. § 103

The Examiner has maintained the rejection of claims 1, 2, 8, 13-14, 17-20, 28, 36, and 38-40 and has newly rejected claim 41 under 35 U.S.C. § 103 as allegedly unpatentable over Wu *et al.*, U.S. Patent No. 5,166,320 in view of Rossi *et al.*, U.S. Patent No. 5,144,019 and Hirsch *et al.*, U.S. Patent No. 5,428,132. For the reasons set forth below, Applicants respectfully traverse the Examiner's rejection.

The claimed invention is directed, generally, to protein-polycation conjugates capable of forming complexes with DNA, wherein the protein is capable of targeting the conjugate to cells of the T-cell lineage and wherein the protein is not transferrin. The Examiner has asserted that the claimed subject matter is unpatentable based on the following allegations:

(a) the use of antibody-polylysine-DNA conjugates for the introduction of genes into mammalian cells was known in the art (Wu *et al.*);

(b) the delivery of ribozymes to CD4+ T cells using liposomes to treat HIV infected cells was known in the art (Rossi *et al.*);

(c) the use of anti-CD3 antibody-polynucleotide conjugates to transfect T cells with DNA was known in the art (Hirsch *et al.*);

(d) there was a motivation to combine elements (a)-(c) because it was known in the art that the use of antibody-polylysine-DNA conjugates were advantageous delivery systems to liposomes, (Wu *et al.*);

(e) there was a motivation to combine elements (a)-(c) because it was known in the art that non-covalently conjugating the polynucleotide to polylysine allows for the nucleotide not to be damaged or altered so that successful in vivo endocytosis and expression can occur (Wu *et al.*); and

(f) there was an expectation of success in combining (a)-(c) because antibody conjugating methods were known in the art and methods of linking polynucleotides to polylysine were known in the art.

Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to *particular* sources of information, to select *particular* elements, and to combine them in the way they were combined by the inventor. *ATD Corp v. Lydall, Inc.*, 159 F.3d 534 (Fed. Cir. 1998).

The Examiner has indicated that Rossi *et al.* teach the introduction and delivery of ribozyme genes to CD4+ T cells with a liposome-ribozyme targeting system to treat HIV infected cells. (Paper No. 45, page 3.) The Examiner has also alleged that it was known in the art that "antibody-polylysine-polynucleotide conjugates [were] advantageous delivery systems to liposomes." (*Id.*) Indeed, as the Examiner has suggested, Wu *et al.* teach that liposome gene delivery systems have "inherent problems" and that the object of their invention is to provide "new and improved carrier system[s]." (Column 1, lines 46, 56.) Yet, to indicate that there are general disadvantages associated with the use of one type of gene-delivery method does not provide a suggestion to utilize another type of method. The state of the art was such that virtually all gene delivery systems were characterized by at least some problems. *See, e.g.*, Verma & Somia, *Nature 389*:239-42 (1997) (Exhibit A); W.F. Anderson, *Nature 392(Suppl.)*:25-30 (1998) (Exhibit B). Also, even if one particular method (e.g., antibody-polylysine-polynucleotide conjugates) is *generally* deemed superior to another (e.g., liposome-mediated gene delivery) by those skilled in the art, that does not necessarily mean that that particular method is more advantageous for a *particular* application and that it would not have certain disadvantages in particular applications. *See id. See also* C. P. Hodgson, *Bio/Technology 13*: 222-25

(1995) (Exhibit C). Nowhere in Rossi *et al.*, Wu *et al.* or Hirsch *et al.* is there a teaching or suggestion that protein-polycation conjugates would be effective for the problem of delivering and introducing genes into cells of the T-cell lineage. "A general incentive does not make a particular result obvious, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). Because there is no particular teaching that leads one of ordinary skill in the art to arrive at the claimed invention, Applicants assert that the claimed compositions are not obvious.

Assuming, *arguendo*, that in dealing with the problem of delivering ribozymes to T-cells, one skilled in the art were to look for gene-delivery systems other than those mediated by liposomes, there is nothing in Rossi *et al.* that would lead one skilled in the art to the antibody-lysine-polynucleotide system taught in Wu *et al.* Other gene delivery systems were known in the art besides polycation gene delivery systems and include, for example, calcium phosphate, DEAE Dextran, cell fusion, viral vector delivery systems, gene-gun delivery systems, naked DNA delivery systems, microinjection delivery systems, and microbombardment delivery systems. The Examiner has not indicated why one skilled in the art would be motivated to use the particular gene-delivery method involving polycation-protein conjugates, as described in the claims, in view of the many other possible methods that could be employed by one of ordinary skill in the art. In fact, Rossi *et al.* teach that the alternatives to their liposome-mediated ribozyme delivery methods are cellular transfection methods, calcium phosphate methods, lipofection, electroporation, or the use of a retroviral vector. (Column 6, lines 65-67.) A prior art reference must be considered in its entirety, i.e. as whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). Thus, there is clearly no suggestion in Rossi *et al.* to use a polycation-protein conjugate based system for delivery of ribozymes to T-cells.

Moreover, while Wu *et al.* teach that the *object* of the invention disclosed in their patent is to provide a "new and improved carrier system," they do not teach that their polycation-protein conjugates are, *in fact*, new and improved over the other methods known in the art. Thus, the Examiner's statement that it was known in the art that "antibody-polylysine-polynucleotide conjugates [were] advantageous delivery systems to liposomes" is untrue. (Paper No. 45, page 3.) An object of the invention is the goal that is to be achieved by the invention and there is no indication in Wu *et al.* that their stated objective was met for all cell types and all therapeutic genes in all applications. Wu *et al.* provide no comparative data which demonstrates their claimed methods and compositions are superior to other gene-delivery methods and in particular, they make no claims that their method is superior to liposome-mediated delivery. They also make no claims that their gene-delivery method is superior for introduction of DNA into cells of the T-cell lineage. That the system works for select applications in hepatomic cells is the full extent of the teaching in Wu *et al.* and their statements that the system could be used for other mammalian cells is only conjecture. Thus, while it may have been "obvious to try" the methods of Wu *et al.* in order to improve upon liposome-mediated delivery, obvious to try is not the appropriate standard. *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).

The Examiner has also opined that there was a motivation to combine the references because it was known in the art that non-covalently conjugating the polynucleotide to polylysine allows for the nucleotide not to be damaged or altered so that successful *in vivo* endocytosis and expression can occur. But not damaging or altering the nucleotide to be delivered into the cell is the goal of any gene-delivery method so as to maintain the coding integrity of the gene of interest. Why this goal leads one of ordinary skill in the art to the compositions of claimed invention rather than the other known methods of nucleotide delivery, which may have the similar advantage of not damaging or altering the nucleotide has not been explained by the Examiner. Further, while Wu *et al.* indicate that the nucleic acid binding component must be capable of binding without damaging or chemically

altering the gene, there is no indication in Wu *et al.* that non-covalent binding is *more* effective at preventing this undesired effect than covalent binding. Wu *et al.* only indicate that their method of preventing alteration and damage of the DNA is by non-covalent binding. Given the teachings of Wu *et al.* and Hirsch *et al.*, who teach covalent binding of the DNA to the antibody, there is no suggestion or teaching in the cited references that would lead one of ordinary skill in the art to select one over the other.

The Examiner has also asserted that one of ordinary skill in the art would have an expectation of success in combining the references in order to obtain the claimed invention because antibody conjugating methods were known in the art and methods of linking polynucleotides to polylysine were known in the art. Assuming, *arguendo*, that the methods for making the compositions of the claims were well-known in the art, there was no expectation of success that the compositions would be taken up by cells expressing T-cell surface antigens, as required by the claims. Wu *et al.*, while providing experimental data for targeting hepatocytes using asialoglycoproteins, make no indication that their gene-delivery method would be effective for targeting cells of the T-cell lineage using T-cell receptor-specific antibodies. Rossi *et al.* provide no indication that ribozyme genes could be delivered to T-cells using polycation-protein conjugates. Hirsch *et al.*, while teaching antibody-DNA conjugates, provide no expectation of success that the addition of a polycation (which may dramatically increase the surface area, weight and volume of the conjugate) would produce conjugates capable of introducing DNA into cells. Accordingly, there is no expectation of success provided in the cited references.

Applicants assert that the Examiner has "selectively culled" together known elements from the prior art despite the fact that there is no motivation to do so or expectation of success in doing so. As discussed, there is no *particular* teaching or suggestion in any of the references that would motivate one skilled in the art to combine the other references to arrive at the claimed invention and

there is no expectation of success from the prior art that the compositions of the claims would be effective for introduction of genes cells of the T-cell lineage. Thus, Applicants assert that the Examiner has engaged in improper hindsight reasoning to arrive at the claimed invention. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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